POINTS TO CONSIDER

SCIENTIFIC ABSTRACT

Improvements in radiochemotherapy have correspondingly improved the prognosis of patients with Hodgkin's lymphoma. However, patients resistant to the standard therapeutic approaches have a poor outcome. Moreover, life expectancy and quality of life of patients cured of Hodgkin's lymphoma are both significantly reduced by treatment related mortality and morbidity. These limitations of current treatment protocols illustrate the need for more effective and less toxic therapeutic approaches. In Hodgkin's lymphomas up to 49% of specimens have been shown to carry EBV-DNA and express EBV-genes. Our group has successfully generated EBV-specific CTL in patients with EBV-positive Hodgkin's lymphoma. After infusion these CTL home to the tumor sites, persist in the circulation for up to 5 months, and produce transient clinical benefits. In this protocol, lymphoblastoid cell lines (LCL) are used as EBV-antigen presenting cells (APC). LCL activate polyclonal CTL populations that are preferentially directed against the immunodominant EBNA3A, 3B and 3C EBV-proteins. These immunogenic proteins are not expressed in Hodgkin-Reed-Sternberg (HRS) cells. Instead, the EBV-antigens on HRS cells are restricted to the expression of a subset of latent proteins, EBNA1, LMP1, LMP2A and BARF0. LCL have limited efficacy in stimulating CTL directed against these subdominant proteins. LMP2A epitopes were shown to be conserved among Hodgkin's lymphoma biopsy samples displaying little heterogeneity between viral strains. Also most donors have a low but measurable frequency of circulating LMP2A-specific CTL that can be activated and expanded in vitro. Hence LMP2A may be the protein of choice to be targeted by CTL in patients with Hodgkin's lymphoma. A promising strategy to stimulate LMP2A-specific CTL is the genetic modification of DC that direct the CTL response to virally transduced genes. This approach allows expression of the whole protein leading to presentation of multiple, undefined antigen epitopes. Hence we plan to use a recombinant adenovirus encoding LMP2A for transduction of DC. These genetically modified DC will be used as antigen presenting cells to generate LMP2A-specific CTL in vitro. The resulting LMP2A specific CTL will subsequently will be used to treat patients with relapsed EBV+ Hodgkin's lymphoma.

These LMP2A specific CTL will be marked with a retroviral vector LN encoding the neomycin resistance gene so their persistence can be compared with that of polyclonal EBV specific CTLs generated using LCL as the antigen presenting cell.